REMARKS

Entry of the foregoing and further and favorable reconsideration of the instant application, pursuant to and consistent with 37 C.F.R. §§ 1.116 and 41.202, are respectfully requested.

Status

As is correctly reflected in the Office Action Summary, Claim 275 is the only pending claim in this application. *See Office Action mailed February 13, 2006, Office Action Summary, Item 4.* Claim 275 stands rejected. *Id. at Item 6.* The drawings filed on August 25, 2003, have been accepted by the Examiner. *Id. at Item 10.*

Support for the Amendments

Support for the phrase "aligned substrate nucleic acid sequences" and for "segment boundaries" can be found at least at:

Page 12, Lines 22-23, of the Specification as originally filed (emphasis added):

> Figure 2 depicts the **alignment of alpha interferon amino acid and nucleic acid sequences.**

See, Page 91, Line 19 to Page 92, Line 19, of the Specification as originally filed (emphases added):

> **A. Complexity of the Sequence Space**
>
> Figure 2 shows the protein sequences of 11 human IFN-α's. The differences from consensus are indicated. Those positions where a degenerate codon can capture all of the diversity are indicated with an asterisk. **Examination of the aligned sequences** reveals that there are 57 positions with two, 15 positions with three, and 4 positions with four possible amino acids encoded in this group of alpha interferon genes. Thus, the potential diversity encoded by permutation of all of this naturally occurring diversity is: $2^{57} \times 3^{15} \times 4^4 = 5.3 \times 10^{26}$. Among these hybrids, of the 76 polymorphisms spread over a total of 175 sites in the 11 interferon genes, 171 of the 175 changes can be

incorporated into homologue libraries using single degenerate codons at the corresponding positions. For example, Arg, Trp and Gly can all be encoded by the degenerate codon [A,T,G]GG. Using such a strategy, 1.3×10^{25} hybrids can be captured with a single set of degenerate oligonucleotides. As is evident from Tables III to VI, 27 oligonucleotides is sufficient to shuffle all eleven human alpha interferons. Virtually all of the natural diversity is thereby encoded and fully permuted due to degeneracies in the nine "block" oligonucleotides in Table V.

B. Properties of a "Coarse Grain" Search of Homologue Sequence Space

The modelled structure of IFN alpha (Kontsek, Acta Vir. 38:345-360 (1994)) has been **divided into nine segments based on a combination of criteria of maintaining secondary structure elements as single units and placing/choosing placement of the segment boundaries in regions of high identity.** Hence, one can capture the whole family with a single set of mildly degenerate oligonucleotides. Table III and Figure 2 give the precise locations of these boundaries at the protein and DNA levels respectively. It should be emphasized that this particular segmentation scheme is arbitrary and that other segmentation schemes could also be pursued. The general strategy does not depend on placement of recombination boundaries at regions of high identity between the family members or on any particular algorithm for breaking the structure into segments.

Applicants note that in a previous Response, they referred to support in the specification as follows:

Page 38, Line 18 to Page 39, Line 18 of the Specification as originally filed (emphases added):

> In some embodiments of the invention, a search of a region of sequence space defined by a set of substrates, such as members of a gene family, having less than about 80%, more typically, less than about 50% homology, is desired. This region, which can be part or all of a gene or a gene is arbitrarily delineated into segments. **The segment borders can be chosen randomly, based on correspondence with natural exons, based on structural considerations (loops, alpha helices, subdomains, whole domains, hydrophobic core, surface, dynamic simulations), and based on correlations with genetic mapping data.**
>
> Typically, the segments are then amplified by PCR with a pool of "bridge" oligonucleotides at each junction. Thus, if the set of five genes is broken into three segments A, B and C, and if there are five versions of each segment (A1, A2, . . . C4, C5), twenty five oligonucleotides are made for each strand of the A-B junctions where each bridge oligo has 20 bases of homology to one of the A and one of the B segments. **In some cases, the number of required**

> **oligonucleotides can be reduced by choosing segment boundaries that are identical in some or all of the gene family members.** Oligonucleotides are similarly synthesized for the B-C junction. The family of A domains is amplified by PCR with an outside generic A primer and the pool of A-B junction oligonucleotides; the B domains with the A-B plus the B-C bridge oligonucleotides, and the C domains with the B-C bridge oligonucleotides plus a generic outside primer. Full length genes are made then made by assembly PCR or by the dUTP/uracil glycosylase methods described above. Preferably, products from this step are subjected to mutagenesis before the process of selection and recombination is repeated, until a desired level of improvement or the evolution of a desired property is obtained. This is typically determined using a screening or selection as appropriate for the protein and property of interest.
>
> **An illustration of this method is illustrated below for the recombination of eleven homologous human alpha interferon genes.**

Applicants regret that the Examiner may have previously misinterpreted a portion of the above disclosure. The inaccurate interpretation of the disclosure was discussed during the July 19th interview. Specifically, in Paragraph 219 of the disclosure, it is stated that **"[t]he segment borders can be chosen randomly, based on correspondence with natural exons, based on structural considerations (loops, alpha helices, subdomains, whole domains, hydrophobic core, surface, dynamic simulations), and based on correlations with genetic mapping data."** (Emphasis added). As discussed during the interview, the Examiner appeared to have previously interpreted all of the bolded language as describing "random" choice of segment borders. However, as noted by Applicants' representative during the interview, the bolded section actually refers to several different choices of methods for choosing segment boundaries, with "random" choice being only the first method. Indeed, choosing "based on correspondence with natural exons" is a second method, "based on structural considerations" is a third method, and "based on correlations with genetic mapping data" is yet a fourth method. As such, the previous amendment did not introduce "new matter," because choosing boundaries based upon an alignment of sequences was never

meant to be a description of a "random" method. Examiner Lu understood this distinction during the interview, and agreed with Applicants' explanation of this disclosure.

Interviews

Applicants and their undersigned representative thank Examiner Lu and his colleagues for the courtesies extended during the telephonic interview conducted on July 6, 2006, and during the personal interview conducted on July 19, 2006.

As is correctly reflected in the Interview Summary mailed July 17, 2006, and its Continuation Sheet, Claim 275 was discussed during the telephonic interview. Prior to the telephonic interview, Examiner Lu discussed Applicants' proposed amendment with Quality Assurance Specialist Mr. Christopher Low. "Mr. Low and the examiner agreed that, if applicant agreed to remove 'boundaries defining' in line 8 and 'comprised of' in line 13 of the proposed claim and change 'chimerized but define[d] polynucleotide sequences' in line 11 of the proposed claim to 'chimerized, define[d] polynucleotide sequences', the proposed claim would have no issues on new matter and 112, second paragraph."

As is correctly reflected in the Interview Summary mailed July 24, 2006, a personal interview among Examiner Lu, Mr. Shukla (SPE 1634), Mr. Low (Quality Assurance Specialist), Dr. Sharon Crane, and Ms. Fujita (who participated via telephone) was conducted on July 19, 2006. During the personal interview, Claim 275 and U.S. Patent No. 5,811,238 to Stemmer et al. ("Stemmer") were discussed. As is correctly reflected in the Interview Summary mailed July 24, 2006, Examiner Lu, Mr. Low, and Mr. Shukla agreed that, in view of the proposed amendment to Claim 275 (reproduced above), the "new matter rejection and the rejection under 112, second paragraph have been overcome. Since Stemmer et al., do not teach that boundaries defining the polynucleotide segments are selected from the aligned

substrate nucleic acid sequence, the rejection under 35 USC 102 has [also] been overcome." Note that the amendments agreed upon during the July 19th interview differ from those originally suggested by Mr. Low.

Summary of Claim Amendment

By the foregoing claim amendment, Applicants have amended Claim 275 as proposed during the July 19, 2006, personal interview. Applicants submit that support for the amendment to Claim 275 can be found throughout the Specification and that no new matter has been added.

Rejection Under 35 U.S.C. § 112, First Paragraph – New Matter

Claim 275 was rejected under 35 U.S.C. § 112, First Paragraph, as purportedly containing new matter. *See Office Action mailed February 13, 2006, Pages 2-3, ¶¶ 2-3.* This rejection is respectfully traversed.

Not to acquiesce in the Examiner's rejection, but solely to facilitate prosecution, Applicants have amended Claim 275 in a manner such that the Examiner and his colleagues agree that Claim 275 presents no new matter. *See "Interview" section, above.* Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, Second Paragraph – Indefiniteness

Claim 275 was rejected under 35 U.S.C. § 112, Second Paragraph, as purportedly indefinite. *See Office Action mailed February 13, 2006, Page 3, ¶¶ 4-6.* According to the Examiner, Claim 275 was vague and indefinite due to step (a) "because it is unclear how borders defining the polynucleotide segments can be selected by aligning substrate nucleic

acid sequences because aligning substrate nucleic acid sequences can not find the borders for the polynucleotide segments since the polynucleotide segments is smaller than substrate nucleic acid sequences." *Id.* This rejection is respectfully traversed.

Not to acquiesce in the Examiner's rejection, but solely to facilitate prosecution, Applicants have amended Claim 275 in a manner such that the Examiner and his colleagues agree "the rejection under 112, second paragraph [has] been overcome." *See "Interview" section, above.* Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 102(e) Over U.S. Patent No. 5,811,238 to Stemmer *et al.*

Claim 275 was rejected under 35 U.S.C. § 102(e) as purportedly anticipated by U.S. Patent No. 5,811,238 to Stemmer *et al.* ("Stemmer"). *See Office Action mailed February 13, 2006, Pages 3-5, ¶¶ 7-8.* This rejection is respectfully traversed.

Not to acquiesce in the Examiner's rejection, but solely to facilitate prosecution, Applicants have amended Claim 275 in a manner such that the Examiner and his colleagues agree that "[s]ince Stemmer et al., do not teach that boundaries defining the polynucleotide segments are selected from the aligned substrate nucleic acid sequence, the rejection under 35 USC 102 has [also] been overcome." *See "Interview" section, above.* Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103(a) Over WO 95/22625 to Stemmer

Claim 275 was rejected under 35 U.S.C. § 103(a) over WO 95/22625 to Stemmer ("the Stemmer PCT"). *See Office Action mailed February 13, 2006, Pages 6-8, ¶¶ 9-10.* This rejection is respectfully traversed.

The Examiner indicated that Applicants' remarks filed November 17, 2005, were not

persuasive "toward the withdrawal of the rejection [since] . . . the phrase 'borders defining the polynucleotide segments is selected by aligning substrate nucleic acid sequences' recited in claim 275 is a new matter." *See Office Action mailed February 13, 2006, Page 8.* Not to acquiesce in the Examiner's rejection, but solely to facilitate prosecution, Applicants have amended Claim 275 in a manner such that the Examiner and his colleagues agree that Claim 275 presents no new matter. *See "Interview" section, above.* Accordingly, Applicants respectfully request withdrawal of this rejection.

Renewed Request For Interference

Applicants present this Amendment and Response in conjunction with a Request by Applicants for Interference Pursuant to 37 C.F.R. § 41.202. Applicants present herein a proposed Count and a complete showing of the information required by 37 C.F.R. § 41.202 with regard to the application as presently amended. The required information is set forth below under headings that correspond to the subsections of 37 C.F.R. § 41.202. In order to faciliate consideration of the Renewed Request for Interference by the Examiner, the Appendices attached hereto, whose content is summarized in the following table, further support Applicants' required showings under 37 C.F.R. § 41.202.

Accordingly, Applicants respectfully request that an interference be declared between the instant application and the U.S. Patent No. 6,605,449 to Short ("the Short '449 patent").

TABLE OF APPENDICES:

Appendix A: Exemplary support in the instant application for Claim 275, as amended in the instant amendment

Appendix B: A proposed Count

Appendix C: A side-by-side comparison of Claims 1-12 of the Short '449 patent and the proposed Count

Appendix D: A side-by-side comparison of Claim 275, as amended in the instant amendment, and the proposed Count

Appendix E: A copy of the Short '449 patent

Appendix F: A copy of the instant application, U.S. Patent Application Serial No. 10/646,221 to Patten *et al.*

Appendix G: A comparison of the relative filing dates for Short and Patten

REQUEST FOR INTERFERENCE

I. IDENTIFICATION OF A PATENT THAT INCLUDES SUBJECT MATTER THAT INTERFERES WITH THIS APPLICATION

A patent that claims subject matter that interferes with subject matter claimed in the present Patten '221 application is: U.S. Patent No. 6,605,449 by Short ("the Short '449 patent") for "SYNTHETIC LIGATION REASSEMBLY IN DIRECTED EVOLUTION." The Short '449 patent issued from U.S. Application Serial No. 09/594,459, filed June 14, 2000 ("the Short '459 application"). On the face of the Short '449 patent, the 'Short '459 patent is indicated to be a continuation-in-part of Application Serial No. 09/332,835, filed on June 14, 1999 ("the Short '835 application"), now abandoned. Diversa Corporation, San Diego, California, is identified as assignee on the face of the Short '449 patent.

II. PRESENTATION OF A PROPOSED COUNT

The interfering subject matter between the Patten '221 application and the Short '449 patent relates to methods of producing libraries of chimerized enzymes. Attached Appendix B sets forth a proposed Count in chart form for the Examiner's consideration.

The proposed Count is an alternative Count, prepared after consideration of the subject matter claimed by the respective parties, which describes the interfering subject matter. The proposed Count comprises, in the alternative, Claim 6 of the Short '449 patent, or Claim 275 of the Patten '221 application. The alternative claims which comprise the count describe the same invention within the meaning of 37 C.F.R. § 41.203(a) as shown by comparison of the claims in Appendix B, and further demonstrated by the analysis in Section III below.

III. THE PROPOSED COUNT INCLUDES DIFFERENT TERMS USED BY THE RESPECTIVE PARTIES TO DESCRIBE THE SAME INVENTION

The proposed Count is in alternative form in part because of the different language utilized by the respective parties to describe the interfering subject matter. A comparative analysis of the language used in the respective specifications is presented below.

A. "Progeny library" v. "library"

The Short '449 patent describes progeny molecules as those molecules "obtained by mutagenization of the parental set". (Col. 24, ll. 5-10) The Patten '221 application states that "starting DNA segments are recombined...to generate a diverse library of recombinant DNA segments. In general, the starting segments and the recombinant libraries generated include full-length coding sequences..." (p. 16, ll. 18-25) As such, the "progeny library" of Short and the "library" obtained by mutagenizing the starting DNA segments are the same.

B. "Predetermined polynucleotide sequence" v. "defined polynucleotide sequence"

The Short '449 patent states that "non-stochastic or non-random mutagenesis is exemplified by a situation in which a progenitor molecular template is mutated (modified or changed) to yield a progeny molecule having one or more **predetermined** mutations." (Col. 2, ll. 48-52; Emphasis added.) The Patten '221 application states that "'Coarse grain shuffling' generally involves the exchange or recombination of segments of nucleic acids, whether **defined** as functional domains, exons, restriction endonuclease fragments, or otherwise arbitrarily **defined** segments." (p. 12, l. 35 – p. 13, l. 2) As such, the "predetermined sequences" of the Short '449 patent and the "defined sequences" of the Patten '221 application are the same, because they both relate to the knowledge of the desired mutation prior to making the mutation.

C. "Building block sequences" v. "polynucleotide segments"

The Short '449 patent states that the "building block sequences" may be single-stranded or double-stranded polynucleotides. (Col. 10, ll. 11-12) The Short '449 patent further states that "a unique overall assembly order can also be achieved... by stepping the assembly of the building blocks in a deliberately chosen sequence". (Col. 11, l. 67 – Col. 12, l. 5) Likewise, the Patten '221 application notes that "segments of nucleic acids" can be "defined as functional domains, exons, restriction endonuclease fragments, or otherwise arbitrarily defined segments." (p. 12, l. 35 – p. 13, l. 2) As such, the "building block sequences" of the Short '449 patent and the "defined sequences" of the Patten '221 application are the same, because they both relate to "arbitrarily" or "deliberately" chosen nucleic acid "chunks" which are the starting materials for making the desired end product.

D. "Non-random order" v. "ordered fashion"

The Short '449 patent states that the chimeric nucleic acid molecules are produced non-stochastically, (i.e., non-randomly) such that the "overall assembly order [that] is chosen by design" (e.g., Col. 10, ll. 32-33). Likewise, the Patten '221 application states that the gene segments are reassembled in an "ordered fashion" (p. 33, l. 12). As such, an order which is not random, is "ordered", and therefore the elements of Short Claim 6 and Patten Claim 275 are the same.

E. "Enzymes or fragments thereof' v. "full-length enzymes"

"Full-length enzymes", as recited in Claim 275 of the Patten '221 application are one member of the two-member Markush group of "enzymes or fragments thereof" recited in Claim 6 of the Short '449 patent. Applicants submit that the application of the claimed method to "fragments" of enzymes is not patentable, and as such, Applicants did not add that recitation to Claim 275. Because the "full-length" enzymes of Claim 275 of the Patten '221

application are coextensive with the "enzymes" of Claim 6 of the Short '449 patent, this element of the claims should be considered to be substantially the same, and thus, reflecting interfering subject matter between the Short '449 patent and the Patten '221 application.

F. "Sequences delineated by demarcation points selected from aligned progenitor sequences" v. "boundaries defining the polynucleotide segments are selected from the aligned substrate nucleic acid sequences"

The Short '449 patent discusses determining the ends of what will be "building block" sequences, by aligning a number of substrates and looking for homology therebetween:

> Thus according to one aspect of this invention, the sequences of a plurality of progenitor nucleic acid templates are aligned in order to select one or more demarcation points, which demarcation points can be located at an area of homology, and are comprised of one or more nucleotides, and which demarcation points are shared by at least two of the progenitor templates. The demarcation points can be used to delineate the boundaries of nucleic acid building blocks to be generated. Thus, the demarcation points identified and selected in the progenitor molecules serve as potential chimerization points in the assembly of the progeny molecules. (Col. 52, ll. 37-48)

Likewise, the Patten '221 application at p. 38, ll. 18-28, describes the same such process:

> In some embodiments of the invention, a search of a region of sequence space defined by a set of substrates, such as members of a gene family, having less than about 80%, more typically, less than about 50% homology, is desired. This region, which can be part or all of a gene or a gene is arbitrarily delineated into segments. The segment borders can be chosen randomly, based on correspondence with natural exons, based on structural considerations (loops, alpha helices, subdomains, whole domains, hydrophobic core, surface, dynamic simulations), and based on correlations with genetic mapping data.

See also Page 12, Lines 22-23 and Page 91, Line 19 to Page 92, Line 19.

As such, "sequences delineated by demarcation points selected from aligned progenitor sequences" and "boundaries defining the polynucleotide segments are selected from the aligned substrate nucleic acid sequences" are the same.

G. "Non-stochastically reassembling" v. "reassembling"

If reassembly is characterized as either "stochastic" or "non-stochastic", then "non-stochastic" is one of merely two members of a Markush group. "Non-stochastically" reassembling is not a patentable distinction, because, as Short admits, "Currently available technologies in directed evolution include methods for achieving stochastic (i.e., random) mutagenesis and methods for achieving non-stochastic (non-random) mutagenesis." The Patten '221 application discloses that the design for mutagenesis can be random or non-random (see, Section F, above). As such, "non-stochastically reassembling" is not patentably distinct from "reassembling".

H. "Overall assembly order is achieved" v. "reassembled in an ordered fashion"

Achieving an overall assembly order is the same as reassembling in an ordered fashion. *See Section D, above.*

IV. IDENTIFICATION OF CLAIMS OF THE SHORT '449 PATENT THAT CORRESPOND TO THE PROPOSED COUNT

Claim 6 of the Short '449 patent is identical to an alternative of the Proposed Count and should be designated to correspond to the Proposed Count. Further, Claims 1-12 of the Short '449 patent are obvious over the Proposed Count and should also be designated as corresponding to the proposed Count. A comparison of each of these claims with the Proposed Count is presented in Appendix C.

V. THE CLAIMS OF THE PATTEN '221 APPLICATION THAT CORRESPOND TO THE PROPOSED COUNT

Claims 1-15 and 274 of the Patten '221 application have been canceled. Claim 275 corresponds to the proposed count, because it is identical to an alternative of the proposed Count. Claim 275 represents a substantial copy of Claim 6 of the Short '449 patent and would be obvious over the proposed Count. Appendix D provides a side-by-side comparison of pending Claim 275 of the Patten '221 application with the proposed Count.

VI. APPLICANTS WILL PREVAIL ON PRIORITY

The present Patten '221 application was filed on August 22, 2003, and is a continuation of U.S. Application Serial No. 09/559,671, filed April 27, 2000 ("the 'Patten '671 application"), now U.S. Patent No. 6,613,514 ("the Patten '514 patent"), which is a continuation of U.S. Application Serial No. 08/769,062, filed December 18, 1996 ("the Patten '062 application"), now U.S. Patent No. 6,335,160 ("the Patten '160 patent"). Even if Short were granted the benefit of its Short '835 application, filed on June 14, 1999 (from which the Short '459 patent claims to be a continuation-in-part), Patten would still be designated Senior Party in the interference, because its '062 application was filed approximately two and a half years prior to the Short '835 application. Therefore, Patten will clearly prevail on priority.

The specifications of the Patten '221, '671, and '062 applications are essentially identical. As such, exemplary support for Claim 275 in all three applications is provided in Appendix A.

VII. A CLAIM CHART SHOWING EXEMPLARY WRITTEN DESCRIPTION OF THE ADDED CLAIMS IS ATTACHED

Exemplary support for pending Claim 275 can be found throughout the specification and claims as originally filed, at least as shown in Appendix A, attached.

VIII. CHARTS SHOWING CONSTRUCTIVE REDUCTION TO PRACTICE WITHIN THE SCOPE OF THE PROPOSED COUNT ARE ATTACHED

Appendix A, attached, shows exemplary support for Claim 275 in the present application, which is a continuation of the 'Patten '671 application, which is a continuation of the Patten '062 application. The specifications of the Patten '221, '671, and '062 applications are essentially identical. Thus, Appendix A, also serves to show constructive reduction to practice within the scope of the Count in the '221, '671 and '062 applications.

IX. CONCLUSION

Present Claim 275 is substantially copied from Claim 6 of the Short '449 patent, using the corresponding terminology of the Patten '221 application. Claim 275 was added on August 6, 2004, prior to one year after the issuance of the '449 patent on August 12, 2003. As such, Applicants' Claim 275 is not barred by 35 U.S.C. § 135(b).

In view of the foregoing, Applicants respectfully request that an interference be declared employing the proposed Count set forth in attached Appendix B, with Claims 1-12 of the Short '449 patent, and Claim 275 of the present Patten '221 application being designated as corresponding to the proposed Count.

Furthermore, exemplary support in the '062 application for at least one embodiment within the scope of the proposed Count is shown in Appendix A. Since the Patten '221 application was filed December 18, 1996, well prior to the earliest Short '835 application,

filed June 14, 1999, Patten should be designated as senior party. Such action is respectfully requested.

From the foregoing, further and favorable action in the form of a Declaration of Interference is sought. In the event that there are any questions relating to this Amendment And Response Pursuant To 37 C.F.R. § 1.116 And Renewed Request For Interference Pursuant To 37 C.F.R. § 41.202 or to the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (202) 373-6000 so that prosecution of the application may be expedited.

Respectfully submitted,
BINGHAM MCCUTCHEN LLP

Date August 14, 2006 By: Sharon E Crane

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APPENDIX A

EXEMPLARY SUPPORT[1] IN THE PATTEN '221, '671 AND '069 APPLICATIONS FOR CLAIM 275 AS CURRENTLY PENDING

Claim	Exemplary Support
275. A method of producing a library	p. 2, l. 24 – p. 3, l. 5, Claim 16 ("a method...to generate a library..."); p. 16, ll. 18-20 ("starting DNA segments are recombined...to generate a diverse library of recombinant DNA segments")
comprised of chimerized,	p. 31, ll. 32-35 ("nucleic acids encoding protein modules can be exchanged...to generate novel and functional chimeric polyketides"); p. 37, ll. 20-21 ("A library of 10^4 chimeric interferon genes...");
defined polynucleotide sequences	Claim 16 ("a first and second substrate molecules ...comprise defined segments")
each of which is comprised of a defined number of polynucleotide segments	Claim 16 ("a first and second substrate molecules ...comprise defined segments"); p. 32, l. 6 – p. 34, l. 9 (e.g., "assemble multiple segments"); Example III, p. 89, l. 36 – p. 93, l. 9 (e.g., "The modeled structure...has been divided into nine segments based on a combination of criteria of maintaining secondary structure elements as single units and placing/choosing placement of the segment boundaries in regions of high identity.")
that are assembled in an ordered fashion,	p. 33, l. 12 ("are reassembled in an ordered fashion...")
the method comprising:	p. 2, l. 29 ("the method comprising...")
a) generating a plurality of defined polynucleotide segments selected from aligned substrate nucleic acid sequences,	p. 29, ll. 22-27 ("The coarse grain methods allow one to exchange chunks of genetic material between substrate nucleic acids thereby limiting diversity in the resulting recombinants to exchanges or substitutions of domains, restriction fragments, oligo-encoded blocks of mutations, or other arbitrarily defined segments..."); p. 32, ll. 9-11 ("multiple segments that have been separately evolved..."); p. 32, ll. 17-20 ("Boundaries defining segments of a nucleic acid sequence of interest...")

[1] The identified support is merely exemplary, and is not meant to be exhaustive. Applicant reserves the right to cite additional support at a later time, if necessary.

APPENDIX A

wherein said substrate nucleic acids encode full-length enzymes,	p. 43, ll. 18-20 ("this technique can be used to evolve bovine intestinal alkaline phosphatase (BIAP)..."; p. 82, ll. 16-25 ("Evolution of BIAP...the oligonucleotides are assembled into full-length genes as described above."); p. 16, ll. 22-24 ("In general, the starting segments and the recombinant libraries generated include full-length coding sequences...")
and wherein boundaries defining the polynucleotide segments are selected from the aligned substrate nucleic acid sequences; and	p. 12, ll. 22-23 ("Figure 2 depicts the alignment of alpha interferon amino acid and nucleic acid sequences."); p. 32, ll. 17-20 ("Boundaries defining segments of a nucleic acid sequence of interest preferably lie in intergenic regions, introns, or areas of a gene not likely to have mutations of interest; p. 38, ll. 23-28 ("This region, which can be part or all of a gene or a gene is arbitrarily delineated into segments. The segment borders can be chosen randomly, based on correspondence with natural exons, based on structural considerations (loops, alpha helices, subdomains, whole domains, hydrophobic core, surface, dynamic simulations), and based on correlations with genetic mapping data.); p. 91, l. 19 to p. 92, l. 19 ("Examination of the aligned sequences . . . divided into nine segments based on a combination of criteria of maintaining secondary structure elements as single units and placing/choosing placement of the segment boundaries in regions of high identity.")
b) reassembling said defined polynucleotide segments in order	p. 33, l. 12 ("reassembled in an ordered fashion")
thereby producing the library of chimerized, defined polynucleotide sequences,	p. 31, ll. 32-35 ("nucleic acids encoding protein modules can be exchanged...to generate novel and functional chimeric polyketides"); p. 37, ll. 20-21 ("A library of 10^4 chimeric interferon genes..."); Claim 16 ("a first and second substrate molecules ...comprise defined segments")
such that said segments are reassembled in an ordered fashion	p. 33, l. 12 ("reassembled in an ordered fashion")
to produce each chimerized, defined polynucleotide sequence encoding a full-length enzyme, each of which is comprised of a defined number of polynucleotide segments that are reassembled in an ordered fashion.	p. 31, ll. 32-35 ("nucleic acids encoding protein modules can be exchanged...to generate novel and functional chimeric polyketides"); p. 37, ll. 20-21 ("A library of 10^4 chimeric interferon genes..."); Claim 16 ("a first and second substrate molecules ...comprise defined segments")

APPENDIX B

THE PROPOSED COUNT

Claim 6 of the Short '449 patent (incorporating the limitations of Claim 1, from which it depends)	**OR**	**Claim 275 of the Patten '221 application**
A method of producing a progeny library comprised of chimerized but pre-determined polynucleotide sequences each of which is comprised of a pre-determined number of building block sequences that are assembled in non-random order, the method comprising: generating a plurality of pre-determined nucleic acid building block sequences obtained from polynucleotide sequences that encode enzymes or fragments thereof and comprised of sequences delineated by demarcation points selected from aligned progenitor sequences; and non-stochastically reassembling said nucleic acid building block sequences to produce said chimerized but pre-determined polynucleotide sequences, such that a designed overall assembly order is achieved for each of said chimerized but pre-determined polynucleotide sequence.		A method of producing a library comprised of chimerized, defined polynucleotide sequences each of which is comprised of a defined number of polynucleotide segments that are assembled in an ordered fashion, the method comprising: a) generating a plurality of defined polynucleotide segments selected from aligned substrate nucleic acid sequences, wherein said substrate nucleic acids encode full-length enzymes, and wherein boundaries defining the polynucleotide segments are selected from the aligned substrate nucleic acid sequences; and b) reassembling said defined polynucleotide segments in order thereby producing the library of chimerized, defined polynucleotide sequences, such that said segments are reassembled in an ordered fashion to produce each chimerized, defined polynucleotide sequence encoding a full-length enzyme, each of which is comprised of a defined number of polynucleotide segments that are reassembled in an ordered fashion.

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APPENDIX C

CLAIMS OF THE SHORT '449 PATENT THAT CORRESPOND WITH THE PROPOSED COUNT COMPARED WITH THE PROPOSED COUNT

Short '449 Patent Claim	Comparison with the proposed Count
1. A method of producing a progeny library comprised of chimerized but pre-determined polynucleotide sequences each of which is comprised of a pre-determined number of building block sequences that are assembled in non-random order, the method comprising: (a) generating a plurality of pre-determined nucleic acid building block sequences comprised of sequences delineated by demarcation points selected from aligned progenitor nucleic acid sequences; and (b) non-stochastically assembling said nucleic acid building block sequences to produce said chimerized but pre-determined polynucleotide sequences, such that a designed overall assembly order is achieved for each of said chimerized but pre-determined polynucleotide sequence.	Claim 6, which is dependent from, and incorporates all the limitations of Claim 1, is one alternative of the Count. As such, Claim 1 is anticipated by the Count, and should correspond thereto.

APPENDIX C

Short '449 Patent Claim	Comparison with the proposed Count
2. The method of claim 1 where the progenitor nucleic acid sequences comprise sequences derived from an uncultivated organism or an environmental sample.	Claim 6, which is dependent from, and incorporates the limitations of Claim 2, is one alternative of the Count. As such, Claim 2 is anticipated by the Count, and should correspond thereto. Moreover, deriving sequences from an uncultivated organism or an environmental sample would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* Brennan (1996) *Chemical and Eng. News* 74:31-33
3. The method of claim 1 where the progenitor nucleic acid sequences are comprised of genomic nucleic acid sequences.	Claim 6, which is dependent from, and incorporates the limitations of Claim 3, is one alternative of the Count. As such, Claim 3 is anticipated by the Count, and should correspond thereto. Moreover, starting with genomic sequences is a mere design choice, which would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* WO 98/27230[1] at p. 36, ll. 29-31{"The starting exon DNA may be synthesized de novo from sequence information, or may be present in any nucleic acid preparation (e.g., genomic, cDNA, libraries, and so on)."}

1 Note that WO 98/27230 is the 1998 publication of the PCT application corresponding to the present Patten '221 application specification.

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Short '449 Patent Claim	Comparison with the proposed Count
4. The method of claim 1, where the progeny library is comprised of at least 10^{10} different pre-determined progeny molecular sequences.	Claim 6, which is dependent from, and incorporates the limitations of Claim 4, is one alternative of the Count. As such, Claim 4 is anticipated by the Count, and should correspond thereto. Moreover, progeny library is comprised of at least 10^{10} different pre-determined progeny molecular sequences would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* WO 98/27230 at p. 16, ll. 18-22 and p. 91, ll. 26-28{"The starting DNA segments are recombined by any of the recursive sequence recombination formats provided herein to generate a diverse library of recombinant DNA segments. Such a library can vary widely in size from having fewer than 10 to more than 10^5, 10^9, or 10^{12} members." "Thus, the potential diversity encoded by permutation of all of this naturally occurring diversity is: $2^{57} \times 3^{15} \times 4^4 = 5.3 \times 10^{26}$"}

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Short '449 Patent Claim	Comparison with the proposed Count
5. The method of claim 1, where the progeny library is comprised of at least 10^{15} different pre-determined progeny molecular sequences.	Claim 6, which is dependent from, and incorporates the limitations of Claim 5, is one alternative of the Count. As such, Claim 5 is anticipated by the Count, and should correspond thereto. Moreover, progeny library is comprised of at least 10^{10} different pre-determined progeny molecular sequences would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.*, WO 98/27230 at p. 16, ll. 18-22 and p. 91, ll. 26-28{"The starting DNA segments are recombined by any of the recursive sequence recombination formats provided herein to generate a diverse library of recombinant DNA segments. Such a library can vary widely in size from having fewer than 10 to more than 10^5, 10^9, or 10^{12} members." "Thus, the potential diversity encoded by permutation of all of this naturally occurring diversity is: $2^{57} \times 3^{15} \times 4^4 = 5.3 \times 10^{26}$"}
6. The method of any of claims 1-5, where the nucleic acid building block sequences are obtained from polynucleotide sequences that encode enzymes or fragments thereof.	Claim 6 is one alternative of the Count.

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Short '449 Patent Claim	Comparison with the proposed Count
7. The method of any of claims 1-5, where the nucleic acid building block sequences are assembled to produce polynucleotide encoding biochemical pathways from one or more operons or gene clusters of portions thereof.	Claim 7 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, assembling building block sequences to produce polynucleotide encoding biochemical pathways from one or more operons or gene clusters of portions thereof would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.*, WO 98/27230 at p. 13, ll. 9-13{"For example, coarse grain searches are often better suited for optimizing multigene clusters such as polyketide operons, whereas fine grain searches are often optimal for optimizing a property such as protein expression using codon usage libraries."}
8. The method of any of claims 1-5, where the nucleic acid building block sequences are obtained from polynucleotide encoding polyketides or fragments thereof.	Claim 8 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, assembling building block sequences obtained from polynucleotides encoding polyketides or fragments thereof would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.*, WO 98/27230 at p. 13, ll. 9-13 {"For example, coarse grain searches are often better suited for optimizing multigene clusters such as polyketide operons, whereas fine grain searches are often optimal for optimizing a property such as protein expression using codon usage libraries."}

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Short '449 Patent Claim	Comparison with the proposed Count
9. The method of any of claims 1-5, where the nucleic acid building block sequences are obtained from polynucleotide encoding antibodies or antibody fragments or other peptides or polypeptides.	Claim 9 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, obtaining building block sequences from an antibody would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.*, WO 98/27230, p. 40, ll. 35-37 {"For example, this format is preferred for the in vivo affinity maturation of an antibody by RSR."}
10. The method of any of claims 1-5, where the step of (b) non-stochastically assembling said nucleic acid building blocks is performed to generate a display library comprised of polypeptides or antibodies or peptidomimetic antibodies or antibody variable region sequences suitable for affinity interaction screening.	Claim 10 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, generating a display library comprised of antibody regions would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.*, WO 98/27230, p. 66, ll. 1-2 {"For example, the affinity of an antibody for a ligand can be improved using mammalian surface display and RSR."}
11. The method of any of claims 1-5, further comprising the step of (c) screening said progeny library to identify an evolved molecular property.	Claim 11 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, screening for an evolved molecular property would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.*, WO 98/27230, p. 8, ll. 31-33 {"A further aspect of the invention is a method for screening a library of protease mutants to obtain an improved protease..."}

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Short '449 Patent Claim	Comparison with the proposed Count
12. The method of claim 1, where step of (c) is comprised of expression screening to identify an evolved molecular property.	Claim 12 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, expression screening to identify an evolved molecular property would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.*, WO 98/27230, p. 9, ll. 32-34 {"A further aspect of the invention is a method for screening a library of mutants of a DNA substrate encoding a protein for an evolved DNA substrate, comprising: (a) providing a library of mutants, the library comprising an expression vector; (b) transfecting a mammalian host cell with the library of (a), wherein mutant protein is expressed on the surface of the cell; (c) screening or selecting the products of (b) with a ligand for the protein..."}

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APPENDIX D

PENDING CLAIM 275 OF THE PATTEN '221 APPLICATION THAT CORRESPONDS WITH THE PROPOSED COUNT COMPARED WITH THE PROPOSED COUNT

Patten '221 Application Claim	Comparison with the proposed Count
275. A method of producing a library comprised of chimerized, defined polynucleotide sequences each of which is comprised of a defined number of polynucleotide segments that are assembled in an ordered fashion, the method comprising: a) generating a plurality of defined polynucleotide segments selected from aligned substrate nucleic acid sequences, wherein said substrate nucleic acids encode full-length enzymes, and wherein boundaries defining the polynucleotide segments are selected from the aligned substrate nucleic acid sequences; and b) reassembling said defined polynucleotide segments in order thereby producing the library of chimerized, defined polynucleotide sequences, such that said segments are reassembled in an ordered fashion to produce each chimerized, defined polynucleotide sequence encoding a full-length enzyme, each of which is comprised of a defined number of polynucleotide segments that are reassembled in an ordered fashion.	Claim 275 is one alternative of the Count